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Regioselective alkylzirconation of internal alkynes

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Dedicated to Professor Jean-F. Normant on the occasion of his 65th birthday

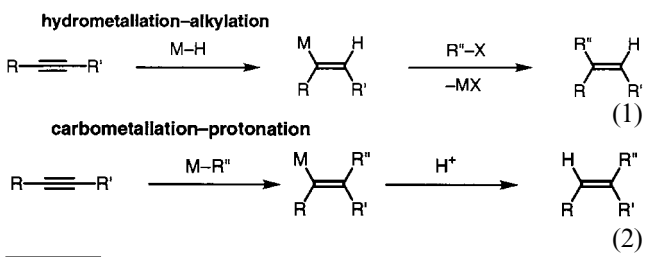
Abstract

Described herein is the carbometallation of unsymmetrically 1,2-disubstituted alkynes with alkylzirconocene complexes, which are generated by hydrozirconation of alkenes. High regioselectivity is achieved when the two substituents of the alkynes are sterically different enough, giving rise to the regio- and stereodefined trisubstituted alkenes. © 2001 Elsevier Science B.V. All rights reserved.

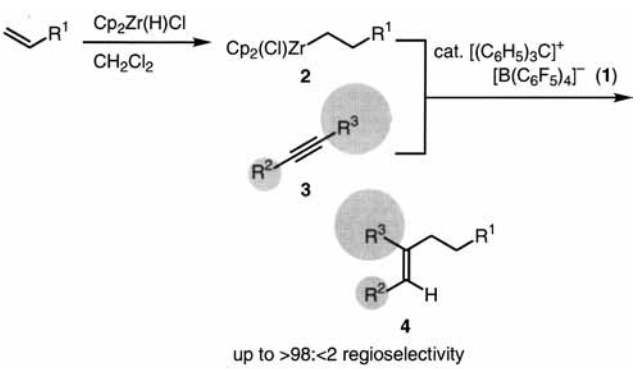
Keywords: Regioselective alkylzirconation; Internal alkynes; Alkylzirconocene complexes

1. Introduction

Alkynes could serve as a useful precursor to various substituted alkenes. The stereoselective reduction of internal alkynes provides ready access to the stereodefined disubstituted alkenes [1]. As for the trisubstituted alkenes, the following optional ways are formally conceivable, that is, (1) hydrometallation followed by further elaboration (Eq. 1), and (2) carbometallation followed by protonolysis (Eq. 2) [2,3].[1] Among these, the latter one has been less exploited so far, due to the limited efficiency of the carbometallation in terms of the reactivity and/or the regioselectivity [2f]. Furthermore, side reactions are sometimes problematic, e.g. reduction by the β-hydride transfer when alkylmetals are employed [4].



We have recently reported the effective alkylzirconation of alkynes in the presence of triphenylcarbenium tetrakis(pentafluorophenyl)borate, $[(C_6H_5)_3C]^+[B(C_6F_5)_4]^-$ (**1**) as an initiator [5,6]. The reaction proved applicable not only to the terminal alkynes, but also to the internal alkynes. At this stage, we became interested in the possibility of applying this protocol to unsymmetrical internal alkynes with a hope of the possible emergence of the regioselectivity [3]. Given the case, a regio- and stereocontrolled access to trisubstituted alkenes would be available (Eq. 3). In this paper, we wish to feature the regioselectivity that is dependent on the difference in the sterics of two substituents, R^2 and R^3.



(3)

* Corresponding author.

[1] Regio- and stereodefined trisubstituted alkenes can also be accesible by the Normant carbocupration of terminal alkynes followed by trapping with electrophiles. See Ref. [1f].

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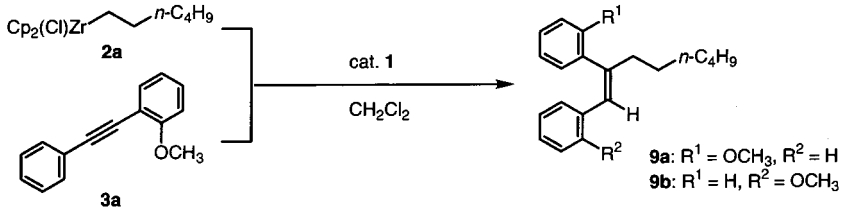
Table 1
Reaction of *n*-hexylzirconocene chloride **2a** with the alkyne **3a**



Run	$[(C_6H_5)_3C]^+[B(C_6F_5)_4]^-$/mol%	Time/h [a]	Yield/% [c] (**9a**:**9b**)
1	20	1.5	87 (94:6)
2	10	3	86 (94:6)
3	5	4	57 (94:6)
4	5	20	61 (94:6) [d]
5	5	20 [b]	52 (96:4) [d]

[a] At 25°C, otherwise noted.
[b] At 40°C.
[c] Combined yields of the regioisomers, whose ratios were assessed by GC. See Section 4.
[d] Two unidentified products (~2%) were also observed by GC.

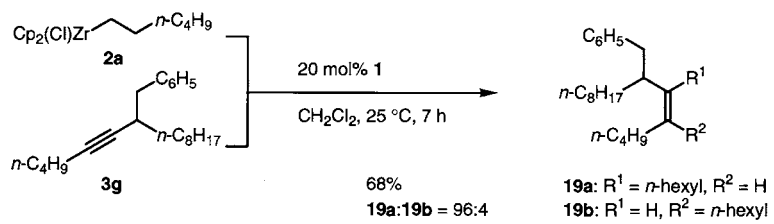
2. Results and discussion

Initially, we examined the reaction of the alkyne **3a** with *n*-hexylzirconocene chloride **2a** (Table 1). To $Cp_2Zr(H)Cl$ (two equivalents) [7] at 25°C was added 1-hexene (two equivalents) in CH_2Cl_2, and the mixture was stirred for 20 min, where a yellow solution resulted. The alkyne **3a** and $[(C_6H_5)_3C]^+[B(C_6F_5)_4]^-$ (20 mol%) were successively added to this mixture, and the stirring was continued for 1.5 h. Quenching with sat. $NaHCO_3$ aq. followed by purification by PTLC gave the regioisomeric alkenes **9a** and **9b** in 87% yield (Table 1, run 1). The major isomer **9a** resulted from the alkyl transfer to the sterically more congested side of the C≡C bond. Attempts at reducing the loading of the trityl salt showed that, though longer reaction time was required, 10 mol% gave a comparable yield (run 2), whereas the rate is impractically slow upon further reduction to 5 mol% (runs 3, 4 and 5).

The 20 mol%-procedure was applied to various alkynes (Table 2). The reactions of the unsymmetrical diarylethynes (**3b** and **3c**), in which the methoxy group on the aromatic ring in **3a** was replaced by Cl or CH_3, were slower, but more regioselective (runs 1 and 2). Particularly, the regioselectivity was perfect for the alkyne **3c** with an *o*-tolyl group. As mentioned above, the alkyl group is delivered to the more hindered site irrespective of the type of the *ortho*-substituent on the aromatic ring. Runs 3–5 show the reaction of the substrates, in which the phenyl group in **3a**–**3c** was replaced by a less bulky n-C_4H_9 group. The regioselectivity showed a parallel tendency observed for **3a**–**3c**, where the reaction rates were considerably faster (runs 3, 4 and 5).

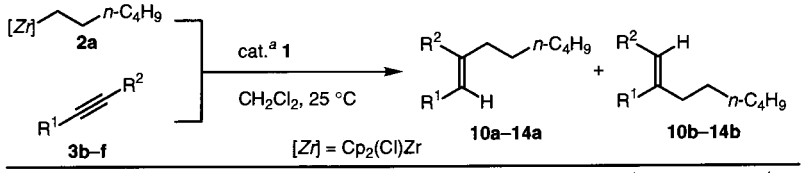
Table 3 illustrates variation of the alkylzirconiums. Notably, the internal C=C bond in the alkylzirconium **2c** remained intact to give the diene product in 88% yield in high regioselectivity (run 2). Functionalized alkyl groups can also be transferred in highly regioselective manner (runs 3 and 4, TBDPS = *t*-butyldiphenylsilyl).

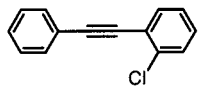
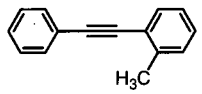
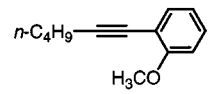
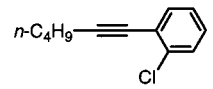
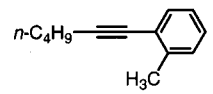
A dialkyl-substituted alkyne also showed high regioselectivity, in case the sterics of the two alkyl groups are sufficiently different. The alkyne **3g** reacted with the *n*-hexylzirconium **2a** in high regioselectivity, although two alkyl substituents are electronically comparable (Eq. 4).



(4)

Table 2
Carbometallation of various disubstituted alkynes with *n*-hexylzirconocene chloride **2a**

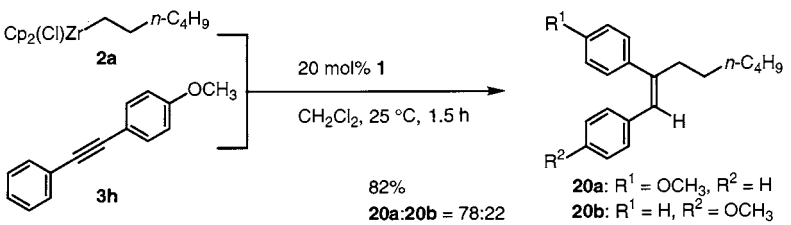


run	R^1—≡—R^2		time/h	yield/%[b]	**a** : **b**[d]
1		(**3b**)	4	75 (**10**)	96 : 4
2		(**3c**)	6	59 (**11**)	>98 : <2
3		(**3d**)	0.25	96 (**12**)[c]	97 : 3
4		(**3e**)	2	71 (**13**)	92 : 8
5		(**3f**)	2	73 (**14**)	>98 : <2

[a] 20 mol% was used, otherwise noted. [b] Combined yields of the regioisomers. [c] 10 mol% of **1** was used. [d] Assessed by GC (see Section 4).

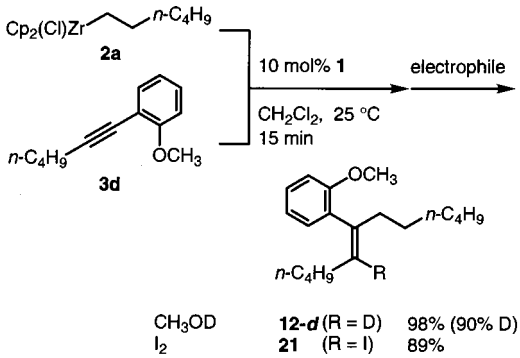
A disubstituted alkyne with electronically different substituents exhibited a moderate regioselectivity. The alkyne **3h**, an isomer of **3a**, was subjected to the carbozirconation reaction with **2a** to give a regioisomeric mixture of **20a** and **20b** in a ratio of 78:22 (Eq. 5). The fact that **20a** was preferred over **20b**, albeit slightly, suggests that the electronic effect is also operating in determining the regioselectivity to some extent.

In order to assess the potential for synthesizing *tetra*-substituted alkenes, quenching of the reaction with electrophiles other than a proton was examined. For example, upon quenching of the reaction of **2a** and **3d** with CH_3OD, the deuterated alkene **12-*d*** was obtained in 98% yield with the 90% D incorporation (Eq. 6). The corresponding iodolysis was also successful by addition



(5)

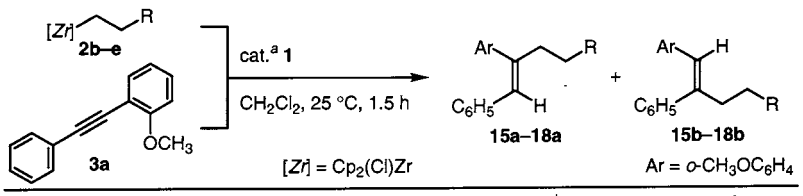
of an I_2 solution in THF dropwise at -60°C. After stirring for 1 h at this temperature, the corresponding iodoalkene **21** was obtained in 89% yield as a single isomer. Such iodoalkenes serve as a useful precursor for regio- and stereodefined tetra-substituted alkenes.[2]

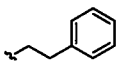
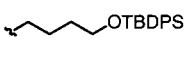
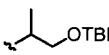


(6)

[2] For selected examples of the coupling reaction with trisubstituted iodoalkenes, see Refs. [3c,8].

Table 3
Carbometallation of the alkyne **3a** with various alkylzirconocene chlorides



run	R		yield/%[b]	a : b[c]
1		(**2b**)	88 (**15**)	94 : 6
2		(**2c**)	88 (**16**)	93 : 7
3		(**2d**)	88 (**17**)	95 : 5[d]
4		(**2e**)	78 (**18**)	95 : 5[d]

[a] 20 mol% was used. [b] Combined yields of the regioisomers. [c] Assessed by GC (see experimental), otherwise noted. [d] Assessed by GC after desilylation with $(n\text{-}C_4H_9)_4NF$ in THF.

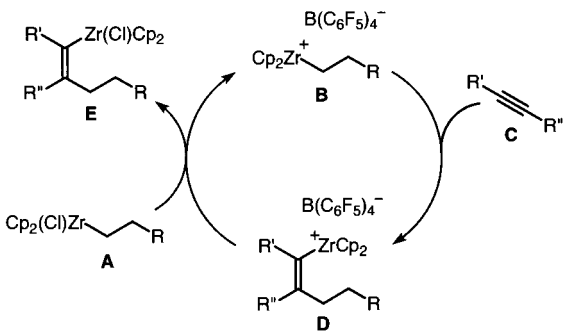
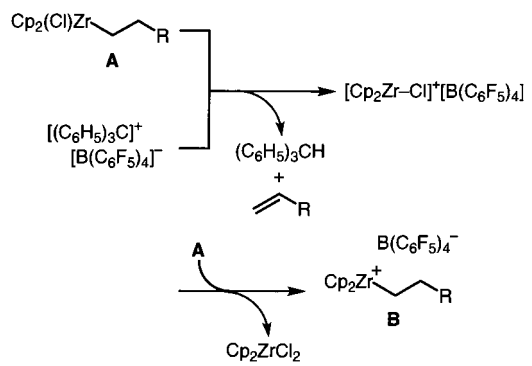


Fig. 1. Proposed catalytic cycle.

Finally, we address the mechanistic consideration. Fig. 1 shows our proposed catalytic cycle. The cationic alkylzirconocene complex **B**, derived from **A** (vide infra), activates the alkyne **C**, enabling the alkyl transfer to give the alkenylzirconocene cation **D**. A chloride exchange between **A** and **D** affords the alkenylzirconocene **E**, thereby regenerating the cationic complex **B**.

Concerning the generation of **B**, it was observed that the trityl portion of the initiator, $[(C_6H_5)_3C]^+[B(C_6F_5)_4]^-$, was mostly converted to $(C_6H_5)_3CH$ by the reaction. This fact suggests that $[(C_6H_5)_3C]^+[B(C_6F_5)_4]^-$ reacts with $Cp_2Zr(R')Cl$ (the β-H abstraction, $R' = -CH_2CH_2R$) to generate a $[Cp_2ZrCl]^+$ species, which, in turn, reacts with $Cp_2Zr(R')Cl$ to form $[Cp_2ZrR']^+$ in **B** as the carrier of this catalytic reaction (Eq. 7) [9].



(7)

3. Conclusion

Carbometallation of unsymmetrical internal alkynes with alkylzirconiums is effected by employing a catalytic amount of $[(C_6H_5)_3C]^+[B(C_6F_5)_4]^-$ (**1**) as the initiator. The regioselectivity was determined mainly by the steric effect of the substituents of alkynes. Success in trapping the alkenylzirconium intermediate with electrophiles provides a promising regio- and stereoselective access to tetrasubstituted alkenes. Further studies are in progress in our laboratory.

4. Experimental

4.1. General

Unless otherwise stated, TC-1 capillary column (GL Sci. Inc., 60 m × 0.25 mm, i.d. 0.25 μm, He 2.0 kgf cm^{-2}) was used for GC analyses. For column chromatography, Merck Silica gel 60 (0.063–0.020 mm) or BW-300 (Fuji Silysia) was used. Preparative thin-layer chromatography (PTLC) was performed on Merck Silica gel 60 PF_{254}. ^{1}H- and ^{13}C-NMR spectra were measured in $CDCl_3$ on a JEOL JNM LA-400 (400/100 MHz) or LA-300 (300/75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane ($\delta = 0$). High resolution mass spectra (HRMS) was obtained with a JEOL JMSAX505HA mass spectrometer. For further information, see Ref. [10].

4.2. Representative procedure for the alkylzirconation is described for the reaction of 1-methoxy-2-phenylethynylbenzene (**3a**) with n-hexylzirconocene chloride (**2a**) (Table 1)

A mixture of $Cp_2Zr(H)Cl$ (147 mg, 0.570 mmol, two equivalents) [8] and 1-hexene (50.8 mg, 0.604 mmol, 2.1 equivalents) in CH_2Cl_2 (2.1 ml) was stirred for 25 min at 25°C. To the resulting yellow solution was added **3a** (59.3 mg, 0.285 mmol, 1.0 equivalents) in CH_2Cl_2 (1.7 ml) followed by $[(C_6H_5)_3C]^+[B(C_6F_5)_4]^-$ (53.0 mg, 0.0575 mmol, 20 mol%). The reaction mixture immediately turned orange in color. After 1.5 h, the reaction was quenched at 0°C by addition of sat. aq. $NaHCO_3$ (0.25 ml) followed by Et_2O (2 ml), and after stirring for 5 min, anhydrous Na_2SO_4 (~ 2.0 g) was added. Filtration through silica gel/Celite pad, evaporation, and purification on PTLC (hexane/EtOAc = 98/2) gave a mixture of the regioisomeric olefins **9a** and **9b** (72.9 mg, 87%) in a ratio of 94:6, assessed by GC (oven temperature 250°C, **9a**: R_t 10.5 min; **9b**: R_t 10.8 min). The E/Z assignment was based on the NOEDIFF data, and the structure was determined, after conversion to alkane **24** via hydrogenation, by the HMQC and HMBC spectra (vide infra).

^{1}H-NMR (the asterisked signals are assigned to **9b**): δ 0.87 (t, 3H, $J = 6.5$ Hz), 1.26–1.47 (m, 8H), {2.47 (t, $J = 7.1$ Hz), 2.53* (t, $J = 7.1$ Hz) (2H)}, {3.72 (s), 3.78* (s) (3H)}, {6.47 (s), 6.61* (s) (1H)}, 6.83–7.28 (m, 9H); ^{13}C-NMR: δ 156.8, 141.1, 137.8, 130.4, 130.2, 128.4, 128.2, 127.7, 126.8, 125.9, 120.8, 111.1, 55.4, 39.6, 31.8, 29.0, 27.9, 22.6, 14.1; IR (neat) 3020, 2925, 2855, 1595, 1490, 1465, 1245, 1030, 750, 695 cm^{-1}; Anal. Calc. for $C_{21}H_{26}O$: C, 85.67; H, 8.90. Found: C, 85.42; H, 9.16%.

Data for other products **10**–**25** (Tables 2 and 3, Eqs. 4–6, Figs. 2 and 3) are presented below.

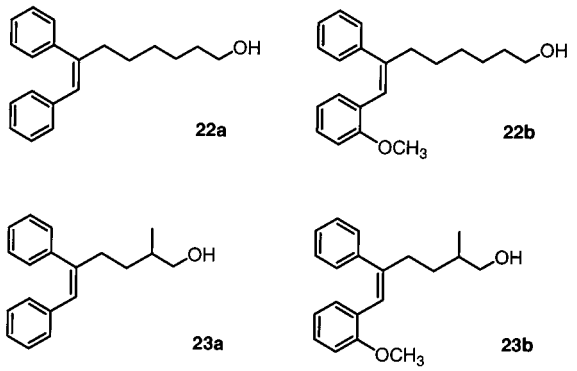


Fig. 2. Structures of **22a**, **22b**, **23a** and **23b**.

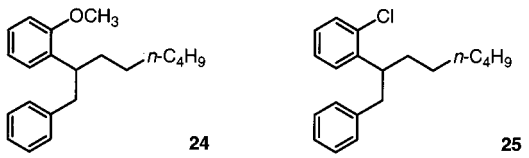


Fig. 3. Structures of **24** and **25**.

4.3. Compound **10a**

As a mixture with the regioisomer **10b**, GC: **10a**: R_t 18.6 min; **10b**: R_t 18.1 min, oven temperature 220°C. For GC analysis, the authentic samples of all four possible isomers were prepared via Wittig olefination. The structure was determined, after conversion to alkane **25** via hydrogenation, by the HMQC and HMBC spectra (vide infra). ^{1}H-NMR (the asterisked signals are the minor peaks assigned to **10b**): δ 0.87 (t, 3H, $J = 6.6$ Hz), 1.27–1.49 (m, 8H), 2.39–2.58 (m, 2H), {6.51 (s), 6.58* (s) (1H)}, 6.80–6.88 (m, 2H), 6.97–7.24 (m, 6H), 7.34–7.42 (m, 1H); ^{13}C-NMR: δ 140.8, 140.3, 137.1, 132.8, 130.6, 129.8, 128.3, 128.2, 127.9, 127.7, 126.9, 126.4, 39.5, 31.7, 29.0, 27.7, 22.6, 14.1; IR (neat) 2955, 2930, 2855, 1600, 1470, 1445, 1035, 745, 695 cm^{-1}; Anal. Calc. for $C_{20}H_{23}Cl$: C, 80.38; H, 7.76. Found: C, 80.34; H, 7.83%.

4.4. Compound **11a**

> 98% Isomeric purity as assessed by GC: R_t 16.0 min, oven temperature 220°C. The structure was determined by the HMQC and HMBC spectral data. ^{1}H-NMR: δ 0.88 (t, 3H, $J = 6.7$ Hz), 1.20–1.51 (m, 8H), 2.10 (s, 3H), 2.34–2.43 (m, 2H), 6.44 (s, 1H), 6.81–6.85 (m, 2H), 7.01–7.09 (m, 4H), 7.13–7.23 (m, 3H); ^{13}C-NMR: δ 142.7, 141.2, 137.6, 135.1, 130.3, 128.5, 128.1, 127.9, 126.9, 126.4, 126.1, 126.0, 40.9, 31.8, 29.2, 27.7, 22.7, 19.3, 14.1; IR (neat) 3020, 2930, 2855, 1600, 1490, 1455, 755, 730, 695 cm^{-1}; Anal. Calc. for $C_{21}H_{26}$: C, 90.59; H, 9.41. Found: C, 90.46; H, 9.61%.

4.5. Compound **12a**

As a mixture with the regioisomer **12b**, GC: **12a**: R_t 7.4 min; **12b**: R_t 8.1 min, oven temperature 250°C. ^{1}H-NMR (the asterisked signals are the minor peaks assigned to **12b**): δ 0.80 (t, 3H, $J = 7.1$ Hz), 0.85 (t, 3H, $J = 6.3$ Hz), 1.16–1.33 (m, 12H), 1.79 (dt, 2H, $J = 7.1$, 7.1 Hz), 2.22–2.35 (m, 2H), {3.78 (s), 3.80* (s) (3H)}, {5.47 (t, $J = 7.1$ Hz), 6.26* (s) (1H)}, 6.86–6.99 (m, 3H), 7.19–7.28 (m, 1H); ^{13}C-NMR: δ 156.7, 138.4, 130.54, 130.46, 127.8, 127.6, 120.1, 110.7, 55.4, 38.2, 32.0, 31.8, 29.0, 28.7, 28.1, 22.7, 22.3, 14.1, 13.9; IR (neat) 2955, 2855, 1600, 1490, 1455, 1245, 1050, 1030, 750 cm^{-1}; Anal. Calc. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.09; H, 11.09%.

4.6. Compound **13a**

As a mixture with the regioisomer **13b**, GC: **13a**: R_t 10.3 min; **13b**: R_t 11.7 min, oven temperature 220°C. ^{1}H-NMR (the asterisked signals are the minor peaks assigned to **13b**): δ 0.80 (t, 3H, $J = 7.1$ Hz), 0.86 (t, 3H, $J = 6.6$ Hz), 1.15–1.42 (m, 12H), {1.68–1.80 (m), 2.09* (t, $J = 7.8$ Hz) (2H)}, 2.16–2.32 (m, 2H), {5.50 (t, $J = 7.3$ Hz), 6.25* (s) (1H)}, 7.02–7.09 (m, 1H), 7.14–7.26 (m, 2H), 7.32–7.41 (m, 1H); ^{13}C-NMR: δ 140.5, 138.7, 132.9, 130.7, 129.3, 128.7, 127.7, 126.2, 38.1, 31.75, 31.68, 29.0, 28.7, 27.8, 22.6, 22.3, 14.1, 13.9; IR (neat) 2930, 2855, 1465, 1435, 1035, 755 cm^{-1}; Anal. Calc. for $C_{18}H_{27}Cl$: C, 77.53; H, 9.76. Found: C, 77.31; H, 10.05%.

4.7. Compound **14a**

$> 98\%$ Isomeric purity as assessed by GC: R_t 12.2 min, oven temperature 200°C. ^{1}H-NMR: δ 0.79 (t, 3H, $J = 7.1$ Hz), 0.86 (t, 3H, $J = 6.7$ Hz), 1.13–1.38 (m, 12H), 1.66–1,74 (m, 2H), 2.15–2.20 (m, 2H), 2.19 (s, 3H), 5.43 (t, $J = 7.2$ Hz), 6.93–6.97 (m, 1H), 7.08–7.19 (m, 3H); ^{13}C-NMR: δ 141.5, 140.5, 135.3, 129.7, 128.9, 127.1, 126.3, 125.2, 39.0, 31.9, 31.8, 29.2, 28.6, 27.9, 22.7, 22.3, 19.3, 14.1, 14.0; IR (neat) 2925, 2855, 1455, 765, 730 cm^{-1}; Anal. Calc. for $C_{19}H_{30}$: C, 88.30; H, 11.70. Found: C, 88.14; H, 11.89%.

4.8. Compound **15a**

As a mixture with the regioisomer **15b**, GC: **15a**: R_t 26.0 min; **15b**: R_t 27.3 min, oven temperature 250°C. ^{1}H-NMR (the asterisked signals are the minor peaks assigned to **15b**): δ 1.40–1.51 (m, 2H), 1.61–1.72 (m, 2H), 2.51 (t, 2H, $J = 7.6$ Hz), 2.58 (t, 2H, $J = 7.8$ Hz), 3.71 (s, 3H), {6.46 (s), 6.62* (s) (1H)}, 6.82–7.28 (m, 14H); ^{13}C-NMR: δ 156.8, 142.8, 140.7, 137.7, 130.2–125.5, 120.8, 111.0, 55.4, 39.3, 35.8, 31.1, 27.5; IR (neat) 3025, 2930, 2855, 1600, 1495, 1465, 1240, 1030, 750, 695 cm^{-1}; Anal. Calc. for $C_{25}H_{26}O$: C, 87.68; H, 7.65. Found: C, 87.62; H, 7.77%.

4.9. Compound **16a**

As a mixture with the regioisomer **16b**, GC: **16a**: R_t 17.0 min; **16b**: R_t 17.9 min, oven temperature 250°C. ^{1}H-NMR (the asterisked signals are the minor peaks assigned to **16b**): δ 1.15–1.26 (m, 1H), 1.33–1.45 (m, 2H), 1.55–1.76 (m, 3H), 2.00–2.13 (m, 3H), 2.52 (t, 2H, $J = 7.9$ Hz), {3.74 (s), 3.80* (s) (3H)}, 5.61–5.68 (m, 2H), {6.48 (s), 6.62* (s) (1H)}, 6.84–7.30 (m, 9H); ^{13}C-NMR: δ 156.8, 141.2, 137.7, 130.4, 130.3, 128.4, 128.2, 127.7, 127.0, 126.8, 126.7, 125.9, 120.8, 111.1, 55.5, 36.8, 34.9, 33.2, 31.9, 28.9, 25.3; IR (neat) 3020, 2915, 2835, 1600, 1575, 1490, 1455, 1240, 1030, 750, 695, 655 cm^{-1}; Anal. Calc. for $C_{23}H_{26}O$: C, 86.75; H, 8.23. Found: C, 87.03; H, 8.46%.

4.10. Compound **17a**

As a mixture with the regioisomer **17b**. The ratio was assessed by GC after conversion to the mixture of **22a** and **22b** by desilylation (vide infra). ^{1}H-NMR (the asterisked signals are the minor peaks assigned to **17b**) δ 1.04 (s, 9H), 1.24–1.59 (m, 8H), 2.45 (t, 2H, $J = 7.0$ Hz), 3.64 (t, 2H, $J = 6.6$ Hz), {3.72 (s), 3.79* (s) (3H)}, {6.46 (s), 6.60* (s) (1H)}, 6.83–7.43 (m, 15H), 7.64–7.68 (m, 4H); ^{13}C-NMR: δ 156.8, 141.0, 137.8, 135.6, 134.2, 130.4, 130.2, 129.5, 128.4, 128.2, 127.7, 127.6, 126.8, 125.9, 120.8, 111.1, 64.0, 55.5, 39.5, 32.6, 29.0, 27.9, 26.9, 25.7, 19.2; IR (neat) 3070, 2930, 1600, 1485, 1455, 1390, 1360, 1240, 1030, 825, 750, 700 cm^{-1}; Anal. Calc. for $C_{37}H_{44}O_2Si$: C, 80.97; H, 8.08. Found: C, 80.96; H, 8.30%.

4.11. Compound **18a**

As a mixture with the regioisomer **18b**. The ratio was assessed by GC after conversion to the mixture of **23a** and **23b** by desilylation (vide infra). ^{1}H-NMR (the asterisked signals are the minor peaks assigned to **18b**): δ 0.94 (d, 3H, $J = 6.8$ Hz), 1.03 (s, 9H), 1.16–1.29 (m, 1H), 1.53–1.79 (m, 2H), 2.39–2.58 (m, 2H), 3.43 (dd, 1H, $J = 9.8$, 6.4 Hz), 3.51 (dd, 1H, $J = 9.8$, 5.6 Hz), {3.69 (s), 3.77* (s) (3H)}, 6.46 (s, 1H), 6.81–7.42 (m, 15H), 7.62–7.66 (m, 4H); ^{13}C-NMR: δ 156.7, 141.1, 137.7, 135.6, 134.1, 130.4, 130.3, 129.4, 128.4, 128.2, 127.7, 127.5, 126.8, 125.9, 120.8, 111.1, 68.8, 55.4, 36.9, 35.3, 31.5, 26.9, 19.3, 16.8; IR (neat) 3070, 2855, 1600, 1495, 1455, 1390, 1360, 1240, 1110, 825, 750, 700 cm^{-1}; Anal. Calc. for $C_{36}H_{42}O_2Si$: C, 80.85; H, 7.92. Found: C, 80.77; H, 8.15%.

4.12. Compound **19a**

As a mixture with the regioisomer **19b**, GC: **19a**: R_t 20.1 min; **19b**: R_t 19.5 min, oven temperature 250°C. ^{1}H-NMR (the asterisked signals are the minor peaks assigned to **19b**): δ 0.83 (t, 3H, $J = 7.1$ Hz), 0.87 (t, 3H, $J = 6.6$ Hz), 0.90 (t, 3H, $J = 6.6$ Hz), 1.00–1.43 (m, 26H), 1.70–1.94 (m, 4H), 2.53–2.66 (m, 2H), 2.78 (tt, 1H, $J = 7.3$, 7.3 Hz), {4.82* (d, $J = 9.0$ Hz), 5.10 (t, $J = 7.1$ Hz) (1H)}, 7.09–7.17 (m, 3H), 7.20–7.25 (m, 2H); ^{13}C-NMR: δ 141.6, 139.8, 129.0, 127.9, 125.8, 125.5, 42.5, 40.7, 32.7, 32.3, 31.94, 31.89, 30.5, 29.8, 29.7, 29.6, 29.3, 28.7, 27.8, 27.2, 22.71, 22.67, 22.5, 14.1 (2C), 14.0; IR (neat) 3025, 2925, 2855, 1605, 1495, 1455, 700 cm^{-1}; Anal. Calc. for $C_{28}H_{48}$: C, 87.42; H, 12.58. Found: C, 87.13; H, 12.80%.

4.13. Compound **20a**

As a mixture with the regioisomer **20b**, GC: **20a**: R_t 12.1 min; **20b**: R_t 12.6 min, oven temperature 250°C. A small amount of pure **20a** could be isolated by the repeated column chromatography on silica gel (twice), for the structural identification by the HMQC and HMBC spectra. ^{1}H-NMR (the asterisked signals are the minor peaks assigned to **20b**): δ 0.87 (t, 3H, $J = 6.8$ Hz), 1.26–1.44 (m, 8H), 2.45 (t, 2H, $J = 7.0$ Hz), {3.70* (s), 3.79 (s) (3H)}, {6.36* (s), 6.39 (s) (1H)}, {6.59*–6.64* (m), 6.92–6.96 (m) (2H)}, 6.79–6.85 (m, 2H), 7.00–7.32 (m, 5H); ^{13}C-NMR (the asterisked signals are the minor peaks assigned to **20b**): δ 158.5, 157.8*, 143.1, 141.8*, 141.6*, 137.8, 133.5, 130.2*, 130.0*, 129.7, 129.0, 128.6*, 128.5*, 127.8, 126.6*, 125.9, 125.8, 125.4*, 113.8, 113.2*, 55.14, 55.08*, 40.7, 31.7, 28.9, 27.9, 22.6, 14.1; IR (neat) 3025, 2930, 2855, 1605, 1510, 1455, 1245, 1035, 835, 750, 695 cm^{-1}; Anal. Calc. for $C_{21}H_{26}O$: C, 85.67; H, 8.90. Found: C, 85.75; H, 9.08%.

4.14. Deuterolysis (Eq. 6)

The carbometallation reaction was carried out with $Cp_2Zr(H)Cl$ (138 mg, 0.535 mmol), 1-hexene (48.3 mg, 0.574 mmol), **3d** (50.1 mg, 0.266 mmol), and $[(C_6H_5)_3C]^+[B(C_6F_5)_4]^-$ (24.7 mg, 0.0268 mmol) in the same manner as that for the preparation of **9a** (See *Representative procedure*). The reaction mixture was stirred for 15 min at 25°C, to which was added CH_3OD (0.5 ml) slowly at 0°C. After stirring for 2.5 h at 25°C, the mixture was worked up as described in Section 4.2. Purification by PTLC (hexane/acetone = 99/1) afforded **12-*d*** (71.8 mg, 98%).

4.15. Compound **12-d**

90% D incorporation assessed by ^{1}H-NMR, ^{13}C-NMR δ 156.7, 138.3, 130.54, 130.48, 127.6, 127.4 (t, $J = 23$ Hz), 120.1, 110.7, 55.3, 38.1, 32.0, 31.8, 29.0, 28.6, 28.1, 22.6, 22.3, 14.1, 13.9.

4.16. Iodolysis (Eq. 6)

The carbometallation reaction was carried out with $Cp_2Zr(H)Cl$ (144 mg, 0.558 mmol), 1-hexene (50.0 mg, 0.595 mmol), **3d** (52.3 mg, 0.278 mmol), and $[(C_6H_5)_3C]^+[B(C_6F_5)_4]^-$ (25.7 mg, 0.0278 mmol) in the same manner as that for the preparation of **9a** (see Section 4.2). The resulting mixture was stirred for 15 min at 25°C, and then chilled to −60°C, to which was added iodine (154 mg, 0.606 mmol) in 3 ml of THF. After stirring for 1 h at this temperature, the reaction was stopped by the addition of sat. aq. $NaHCO_3$. The mixture was extracted ($Et_2O \times 3$), and the organic phase was washed (10% aq. $Na_2S_2O_3$ and brine), and dried over anhydrous Na_2SO_4. Evaporation and the repeated purification (three times) on silica gel (hexane/acetone = 99/1) avoiding exposure to light, gave **21** (99.1 mg, 89%) as a single isomer.

4.17. Compound **21**

> 98% Isomeric purity as assessed by GC: R_t 10.7 min, oven temperature 250°C. ^{1}H-NMR: δ 0.75 (t, 3H, $J = 7.2$ Hz), 0.85 (t, 3H, $J = 6.6$ Hz), 1.06–1.52 (m, 12H), 2.12–2.29 (m, 2H), 2.38–2.59 (m, 2H), 3.77 (s, 3H), 6.85–6.95 (m, 3H), 7.21–7.28 (m, 1H); ^{13}C-NMR: δ 156.1, 142.8, 130.0, 129.0, 128.3, 120.1, 110.7, 108.2, 55.2, 43.4, 41.5, 32.0, 31.7, 29.1, 27.1, 22.6, 21.3, 14.1, 13.9; IR (neat) 2925, 2855, 1595, 1490, 1455, 1245, 1050, 1030, 750 cm^{-1}; Calc. for $C_{19}H_{29}OI$: C, 57.00; H, 7.30. Found: C, 56.90; H, 7.49%.

4.18. Desilylation

Desilylation of the mixture of **17a** and **17b** was performed by the following procedure: To an ice-cooled solution of the mixture of **17a** and **17b** (68.5 mg, 0.125 mmol) in THF (2.0 ml), tetra-*n*-butylammonium fluoride (TBAF) (1.0 M in THF, 0.14 ml, 1.1 equivalents) was added dropwise. After stirring at 25°C for 1.5 h, the reaction was quenched by the addition of a phosphate buffer (pH 7). The mixture was extracted ($Et_2O \times 3$), and the organic phase was washed (2 M HCl, sat. $NaHCO_3$ aq., brine), and dried over anhydrous Na_2SO_4. Evaporation and purification by column chromatography on silica gel (hexane/EtOAc = 98/2) followed by PTLC (hexane/EtOAc = 7/3) gave a mixture of **22a** and **22b** (37.1 mg, 96%, **22a**:**22b** = 95:5 assessed by GC).

4.19. Compound **22a**

As a mixture with the regioisomer **22b**, GC: TC-1701 capillary column, **22a**: R_t 18.4 min; **22b**: R_t 19.3 min, oven temperature 270°C. ^{1}H-NMR (the asterisked signals are the minor peaks assigned to **22b**): δ 1.28–1.58

(m, 9H), 2.48 (t, 2H, $J = 6.8$ Hz), 3.60 (t, 2H, $J = 6.6$ Hz), {3.72 (s), 3.80* (s) (3H)}, {6.47 (s), 6.61* (s) (1H)}, 6.83–7.14 (m, 8H), 7.19–7.28 (m, 1H); ^{13}C-NMR: δ 156.7, 140.8, 137.7, 130.3, 130.2, 128.4, 128.2, 127.7, 126.9, 125.9, 120.8, 111.1, 63.0, 55.4, 39.4, 32.7, 29.0, 27.8, 25.5; IR (neat) 3355, 3020, 2930, 1495, 1485, 1435, 1240, 1025, 750, 695 cm^{-1}; Anal. Calc. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 80.95; H, 8.62%.

In a similar manner, alkene **18** was treated with TBAF (1.6 equivalents, 25°C, 7.5 h) as that for **17** described above, to afford a mixture of **23a** and **23b** (**23a**:**23b** = 95:5 assessed by GC) in quantitative yield.

4.20. Compound *23a*

As a mixture with the regioisomer **23b**, GC: TC-1701 capillary column, **23a**: R_t 14.1 min; **23b**: R_t 14.8 min, oven temperature 270°C. ^{1}H-NMR (the asterisked signals are the minor peaks assigned to **23b**): δ 0.93 (d, 3H, $J = 6.6$ Hz), 1.16–1.74 (m, 4H), 2.41–2.64 (m, 2H), 3.42 (dd, 1H, $J = 10.5$, 6.4 Hz), 3.49 (dd, 1H, $J = 10.5$, 5.9 Hz), {3.72 (s), 3.80* (s) (3H)}, 6.49 (s, 1H), 6.84–7.29 (m, 9H); ^{13}C-NMR: δ 156.8, 140.7, 137.6, 130.3, 130.1, 128.4, 128.3, 127.7, 127.0, 126.0, 120.9, 111.2, 68.2, 55.5, 36.8, 35.4, 31.2, 16.5; IR (neat) 3360, 3020, 2930, 1595, 1485, 1455, 1240, 1025, 750, 695 cm^{-1}; Anal. Calc. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.07; H, 8.41%.

4.21. Hydrogenation

The structure of **9** were identified by means of the HMQC and HMBC spectroscopy after hydrogenation: To a degassed solution of **9** (29.0 mg, 0.0986 mmol) in EtOAc (2 ml)/EtOH (1 ml), 5% Pd/C (8.0 mg, 3.8 μmol, 4 mol%) was added, and stirred under hydrogen (ambient pressure) at 25°C for 0.5 h, after which hydrogen was replaced by argon. Filtration of the mixture, followed by evaporation and purification by PTLC afforded **24** (29.0 mg, quant.).

4.22. Compound *24a*

^{1}H-NMR: δ 0.82 (t, 3H, $J = 6.9$ Hz), 1.09–1.26 (m, 8H), 1.59–1.65 (m, 2H), 2.81 (dd, 1H, $J = 13.5$, 7.5 Hz), 2.85 (dd, 1H, $J = 13.5$, 7.0 Hz), 3.33–3.41 (m, 1H), 3.69 (s, 3H), 6.73–6.91 (m, 2H), 7.04–7.23 (m, 7H); ^{13}C-NMR: δ 157.6, 141.3, 133.7, 129.2, 127.8, 127.6, 126.6, 125.5, 120.5, 110.7, 55.4, 42.6, 39.7, 34.0, 31.8, 29.4, 27.4, 22.6, 14.0; IR (neat) 3025, 2925, 2855, 1600, 1495, 1455, 1240, 1055, 1030, 750, 700 cm^{-1}; Anal. Calc. for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 84.97; H, 9.57%.

In a similar manner, alkene **10** was hydrogenated over 5% Pd/C (3 mol%) at 25°C for 1 h as that for **9** described above, to afford **25** in 76% yield. The reaction should be stopped immediately after the disappearance of **10** was confirmed, otherwise the chloro group would be removed by further reduction. The reaction was monitored by GC analysis.

4.23. Compound *25*

GC: R_t 18.5 min, oven temperature 220°C, cf. **10**. ^{1}H-NMR: δ 0.82 (t, 3H, $J = 7.0$ Hz), 1.11–1.26 (m, 8H), 1.57–1.71 (m, 2H), 2.79 (dd, 1H, $J = 13.5$, 7.7 Hz), 2.89 (dd, 1H, $J = 13.5$, 6.8 Hz), 3.49–3.57 (m, 1H), 7.07–7.32 (m, 9H); ^{13}C-NMR: δ 142.5, 140.3, 134.5, 129.4, 129.2, 128.0, 127.9, 126.9, 126.7, 125.8, 42.6, 42.5, 34.3, 31.7, 29.3, 27.1, 22.6, 14.0; IR (neat) 3025, 2925, 2855, 1605, 1455, 1240, 755, 700 cm^{-1}; Anal. Calc. for $C_{20}H_{25}Cl$: C, 79.84; H, 8.38. Found: C, 79.61; H, 8.68%.

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